

Baxter

11743 '99 JUL 16

July 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Rm. 1-23
Rockville, MD 20857

Re: [Docket No. 98D-0362] Guidance for Industry; Stability Testing of
Drug Substances and Drug Products, Draft, June 1998.

Dear Madam or Sir:

The enclosed comments are being submitted by Baxter Healthcare Corporation in response to the draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products, June, 1998.

Baxter supports all comments submitted July 16, 1999 by the HIMA LVP Systems Task Force and are incorporating them into this correspondence by reference (copy appended). We are also providing additional specific comments from Baxter by section and line number.

We appreciate the opportunity to comment on this draft guideline. If you have any questions regarding our comments, please contact me. We are open to follow-up discussions on these comments and would be willing to meet with the Agency to facilitate discussions if appropriate.

Sincerely,



Marcia Marconi
Vice President Regulatory Affairs
(847) 270-4637
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cc: Bob Seevers, Ph.D.

98D-0362

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Draft Guidance for Industry
Stability Testing of Drug Substances and Drug Products
Specific Comments

SECTION II: STABILITY TESTING FOR NEW DRUG APPLICATIONS

Lines 131-135

“Where *significant change* occurs during 6 months of storage under conditions of accelerated testing at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$, additional testing at an intermediate condition (such as $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$) should be conducted for a drug substance to be used in the manufacture of a dosage form tested for long-term at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ and this information should be included in the drug application.”

This section should allow for the use of an Arrhenius model to assist in predicting if an intermediate condition, e.g. 30°C would be acceptable. If the model indicates that an intermediate condition is expected to fail, additional testing should not need to be performed.

Lines 182-184

“The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale.”

This section implies that a linear regression analysis is required for a degradation relationship, however there may be instances where a linear regression is not appropriate. For example, where absorption occurs, the change in potency over time may be an exponential declining curve with a non-zero asymptote that does not linearize with a logarithmic transformation. An analysis of this type is better suited to a non-linear analysis. Therefore, it is suggested that this guidance allow other forms of mathematical analyses to be used, if appropriate.

Line 339:

“Long-term conditions: $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, with monitoring, but not control of humidity.”

For all other storage conditions in this section, where humidity control is not required, the requirement is stated as ambient humidity. It is suggested that the statement be modified to: “Long-term conditions: $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, with ambient humidity.”

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Line 342: **“• Accelerated conditions: 5°C ± 3°C/ambient humidity.”**

For some drug products such as frozen small volume parenterals, there may be no appropriate long-term accelerated condition for testing of product, i.e. storage at 5°C , or 15°C above the long-term storage temperature, for the extended time frames (i.e. 6 months) as recommended by the Guidance. Supporting information regarding this comment it provided in the attached publication (R. Chilamkurti, J of Parenteral Science & Technology, 46:4 Pp124-129, 1992). These products are thawed just prior to use, and contain label statements identifying both the allowable storage temperatures and time frame.

Lines 545-547 **“The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale.”**

This section implies that a linear regression analysis is required for a degradation relationship, however there may be instances where a linear regression is not appropriate. For example, where absorption occurs, the change in potency over time may be an exponential declining curve with a non-zero asymptote which does not linearize with a logarithmic transformation. An analysis of this type is better suited to a non-linear analysis. Therefore, it is suggested that this guidance allow other forms of mathematical analyses to be used, if appropriate.

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Lines 601-604: **“LVP Solutions packaged in a semi-permeable container (e.g., a plastic bag) and containing simple organic salts (e.g., acetate, citrate, gluconate, and lactate, and dextrose 10 percent or less) may be labeled as above, provided there are adequate stability data (at least 3 months’ at 40°C ± 2°C/15%RH ± 5% or 40°C/NMT 20% RH) to support such labeling.”**

The 40°C excursion statement for LVPs is acceptable. We suggest that this statement be modified to include SVP solutions, as appropriate.

SECTION VII: SPECIFIC STABILITY TOPICS

Lines 1188-1248: **“C. Microbial Control and Quality”**

Lines 1208-1209: **“Chemical assays of preservative content(s) should be performed at all test points.”**

This statement is inconsistent with matrixing and testing of preservatives discussed elsewhere in this Guidance document. Chemical assays should be performed at appropriate test points.

Lines 1346-1447: **“E. Statistical Considerations and Evaluation”**

Lines 1348-1367: **“1. Data Analysis and Interpretation for Long-term Studies”**

Statistical analyses may be a powerful tool in evaluating stability data and providing a high level of confidence with respect to product meeting specifications throughout the expiration dating period. This section describes only one acceptable statistical approach for expiration dating. Statistical procedures that are technically sound should be allowed without prior agency approval.

Lines 1356-1358: **“The methods described in this section are used to establish with a high degree of confidence an expiration dating period during which average drug product attributes such as assay and**

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degradation products of the batch will remain within specifications.”

This section describes only one acceptable statistical approach for expiration dating. There are other statistical approaches available for the evaluation of stability data, which are equally acceptable, and that in some cases are more appropriate for the evaluation of this type of data. It is recommended that a statement be added to allow for use of alternate appropriate statistical approaches.

Lines 2274-2553: **“Section N: Stability Testing of Biotechnology Drug Products”**

This section describes the requirements necessary for the development and submission of new products. The requirements, however, for post-approval changes are not listed in this section or in Section IX. Guidelines applicable to post approval changes for biotechnology drug products need to be described in a guidance document.

Line 2493: **“OCH Q1A”**

Line 2546: **“OCH Q1A”**

Typographical errors should be corrected to read : **“ ICH Q1A”**

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SECTION VIII: CONSIDERATIONS FOR SPECIFIC DOSAGE FORMS

In general, this section presents the types of tests that should be included in a stability study based on the dosage form. Of specific concern are the tests for “odor” and “taste”, for example. It is recognized that there may be instances where a subjective test may be warranted, but they should be the exception, and applied appropriately. Another concern with a subjective test is how the acceptance criteria are established and implemented. Additionally, there may be a safety factor involved with the tasting and smelling of some of these products. This would truly be a concern, from a toxicity standpoint, where testing is identified for products with expected degradation products.

It is recommended that the subjective tests be eliminated or replaced with more quantitative tests, as necessary, in all parts of Section VIII, with testing of this type handled on a case by case basis.

Also, the need to test for pyrogenicity in parenteral solutions defined in sections L and M should only be required at the initial test interval. See response to section VII.C.4 (Lines 1237-1248).

Lines 2612-2620 **“G. Inhalation Solutions and Powders”**

Lines 2612-2615 **“The evaluation of inhalation solutions and solutions for inhalation should include appearance, color, assay, degradation products, pH, sterility, particulate matter, preservative and antioxidant content (if present), net contents (fill weight/volume), weight loss, and extractables/leachables from plastic, elastomeric and other packaging components.”**

This recommended evaluation for “extractables/leachables” is inconsistent with that presented in Section VII.B.3 Container Closure, and should be deleted.

Additionally, the net contents should not be required for stability if net content is a release criteria and weight loss evaluations are conducted.

Lines 2629-2645 **“I. Topical, Ophthalmic and Otic Preparations”**

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Lines 2641-2642 **“Evaluation of ophthalmic and otic products (e.g., creams, ointments, solutions, and suspensions) should include the following additional attributes: sterility, particulate matter, and extractables.”**

The recommended evaluation for extractables is inconsistent with that presented in Section VII.B.3 Container Closure, and should be deleted.

Lines 2654-2684 **“L. Small Volume Parenteral (SVPs)”**

Line 2657-2658: **“Evaluation of *Drug Injection* products should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, and pyrogenicity.”**

We do not believe that there is any value in testing for pyrogenicity during stability (see comments lines 1237-1248), and it is recommended this test be deleted from the list of recommended evaluations.

Line 2665 **“... degradation products/aggregates, sterility, pyrogenicity, and particulate matter.”**

We do not believe that there is any value in testing for pyrogenicity during stability (see comments lines 1237-1248), and it is recommended this test be deleted from the list of recommended evaluations.

Lines 2672-2674 **“The functionality and integrity of parenterals in prefilled syringe delivery systems should be ensured through the expiration dating period with regard to factors such as applied extrusion force, syringeability, pressure rating, and leakage.”**

The requirement to evaluate the functionality of the device aspect of a pre-filled syringe delivery system on stability is not appropriate since these measures have been evaluated during product development and container closure changes. It is recommended that the proposed requirement for function and integrity testing on stability be eliminated from routine stability monitoring.

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Lines 2682-2684

“Interaction of administration sets and dispensing devices with parenteral drug products, where warranted, should also be considered through appropriate use test protocols to assure that absorption and adsorption during dwell time do not occur.”

For clarity we recommend that examples be cited to illustrate when such testing is warranted. The following sentence could be added. “Examples of circumstances where such testing is warranted include drugs with known incompatibility with some dispensing device materials, such as nitroglycerin which adsorbs to polyvinyl chloride tubing or paclitaxel which can extract diethylhexylphthalate plasticizer used in some polyvinyl chloride tubing.”

ATTACHMENT 1

**Draft Guidance for Industry
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Specific Comments**

Attachment 1

Copy of Formulation Development of Frozen Parenteral Dosage Forms

Formulation Development of Frozen Parenteral Dosage Forms

RAO N. CHILAMKURTI

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ATTACHMENT 2

**Draft Guidance for Industry
Stability Testing of Drug Substances and Drug Products
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Attachment 2

Copy of HIMA 7/15/99 Correspondence



July 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Rm. 1-23
Rockville, MD 20857

Re: [Docket No. 98D-0362] Guidance for Industry; Stability Testing of
Drug Substances and Drug Products, Draft, June 1998.

Dear Madam or Sir:

The HIMA Large Volume Parenteral (LVP) Systems Task Force is submitting comments on the draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products, June, 1998. We trust these comments will assist FDA in issuing a refined guidance which will reflect current thinking of both the agency and industry on the information necessary to demonstrate the stability of drug substances and drug products. Comments are also provided regarding site specific stability considerations.

To facilitate FDA review, comments are divided into two parts: (1) a description of general issues; and (2) specific comments by section and line number.

We appreciate the opportunity to comment on this draft guideline. If you have any questions regarding our comments, please contact me. It is our intent to provide desk and electronic copies of these comments to Dr. Seevers. We are providing a desk copy to Dr. Chen relative to her role in ICH discussions and the recommendations included General Comments section on pages 2 - 4. We are open to follow-up discussions on these comments and would be willing to meet with the Agency to facilitate discussions if appropriate.

Sincerely,

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Storage Conditions for Drug Products in Semi-Permeable and Permeable Containers

We recommend that storage conditions for solutions in semi-permeable containers reflect discussions between FDA and the HIMA Large Volume Parenteral (LVP) Task Force. A technical paper supporting the HIMA LVP Task Force position was submitted to Dr. Roger Williams and other FDA representatives on August 24, 1998. A copy of this correspondence is enclosed with these comments for your convenience. We have also reviewed the conditions recommended in a March 1, 1999 correspondence by Dr. J. Curley for discussions within the ICH working group on stability. We incorporate this attached document by reference and believe it is relevant the US stability guidance as well as ICH discussions for products in semi-permeable containers. We understand these most recent storage condition recommendations to be:

- *Long Term Testing:* $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/ 40\% \pm 5\% \text{RH}$ 12 months at submission.
- *Accelerated Testing:* $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/\text{NMT } 25\% \text{RH}$ 6 months at submission.

An alternate approach is to perform the studies, including water loss, under higher relative humidities than those specified above, and derive the water loss at the specified relative humidities through calculation. For example, water loss data obtained at $25^{\circ}\text{C}/60\%\text{RH}$ could be used to calculate the water loss at $25^{\circ}\text{C}/40\%\text{RH}$ for the same container (same material, same size and fill). The assay, expressed as concentration, measured at $25^{\circ}\text{C}/60\%\text{RH}$ is adjusted accordingly to reflect the concentration expected at $25^{\circ}\text{C}/40\%\text{RH}$ on which the expiration date is based. This approach would allow the use of chambers currently specified for storage of solid products.

- *Significant Change for Water Loss:* Water loss greater than 5% in 3 months at or equivalent to NMT 25%RH or in 6 months at 60%RH. A significant change in water loss alone will not necessitate an intermediate study; but it should be demonstrated that such a change does not occur over the proposed shelf life of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\% \pm 5\% \text{RH}$ either by direct measurement of water loss at this condition or from conversion from water loss observed at an alternate humidity condition. If significant change occurs at long-term condition over the proposed shelf life, the container/closure system may not be adequate.
- *Intermediate Testing:* Where a significant change other than water loss occurs during accelerated conditions, additional testing should be conducted at an intermediate, well-defined and controlled temperature. The purpose of this intermediate testing is to evaluate thermal or other effects, thus water loss assessment is not conducted. The initial Registration Application should include a minimum of 6 months' data from a 12-month study.

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The taskforce supports this proposal with the following recommendations:

1. The use of lower relative humidities than the specified conditions should also be allowed and could be incorporated by adding "or lower" to line 35 of Dr. Curley's document after the word "higher". The conditions proposed have varied over the last few years of discussion and some storage areas have been designed with lower relative humidities, e.g. 15% at 40°C rather than 20% or 35% at 25°C rather than 40%. The use of lower relative humidities as a worse case to, or with derivation at, the specified conditions is technically supported by information the task force has previously provided.
2. We believe line 50 of Dr. Curley's document is intended to read "... Water loss greater than 5% in 3 months at or equivalent to NMT 25%RH" rather than "Water loss not greater than 5% in 3 months at or equivalent to NMT 20%RH". We also recommend that line 60 be modified to include "should be conducted".
3. It is presumed that intermediate testing conducted due to significant changes other than water loss under accelerated conditions should be performed at 30°C ± 2°C.
4. It is recognized that the recommendation for 12 months of long-term test data at the time of submission is taken directly from ICH Q1A. However, for some products, particularly those that are not new molecular entities, long-term testing covering 12 months' duration at the time of submission is not warranted and 6 months of testing can be sufficient. Other new NDAs may be for amino acid solutions or LVP multi-chamber products covering combinations of existing solutions. These can also be technically supported with 6 months of data. For products in semi-permeable plastic containers, water vapor transmission rate characterization is very reliable with 6 months of data.

In addition, some of these products have short shelf lives and can be technically defended with less than 12 months of data.

5. A sufficient timeframe for transition should be provided when conditions are finalized. A two-year transition period is recommended.
6. We continue to believe that use of 60%RH is technically justified for long term testing of products intended only for European or Japanese markets, and request that this concept be incorporated into ICH documents.

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7. Please note our specific comment to line 353/4 of the draft US guidance regarding accelerated test stations. For consistency with conditions recommended for semi-permeable containers above, we note that in some cases test stations at 0, 1, 3, and 6 may be preferred.
8. We recommend that the relative humidity recommendations for products in semi-permeable containers be incorporated into Section III of the US guidance regarding ANDAs.

We request the Draft US guidance be revised to incorporate comments 1-5, 7, and 8 for testing of products in semi-permeable plastic containers. We also request comments 1-6 be incorporated into ICH discussions.

Storage Statements

The summary table for uniform storage statements in drug product labeling (Table 2 on line 643-648 of the draft guidance) should be modified to include the appropriate labeling for liquid dosage forms in semi-permeable containers which is described earlier in the text (lines 578-605) or include a reference to this information.

Site Specific Stability Data

The task force shares concerns with others in the pharmaceutical industry regarding the value of, and scientific rationale for, site specific stability data. We believe technology transfer and process validation studies demonstrate conformance to cGMP, support the reproducibility and robustness of the process, and provide assurance that product will meet established specifications. If the specifications are met, and the manufacturing process is shown to be equivalent, there is no technical basis to support the need for product stability data. A correspondence supporting the HIMA position was submitted July 15, 1999. A copy of that correspondence is enclosed with these comments for your convenience.

Format and Organization

We recommend that the section "Application of ICH Stability Study Storage Conditions to Approved Applications" be attached as an addendum. A numbered or legal outline format would be preferred. In addition, the draft should be revised to clearly differentiate between stability requirements during development (registration studies) and those requirements for post marketing or commercial stability studies.

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Mean Kinetic Temperature (MKT)

It is recommended that this section be attached as an addendum since these requirements are not related to requirements for conducting studies and/or evaluating stability data and are defined elsewhere (CFR or USP). The requirements stated here are: a) related to the facilities and controls for holding or warehousing pharmaceutical products; and b) definition, calculation and application of mean kinetic temperature

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SECTION II: STABILITY TESTING FOR NEW DRUG APPLICATIONS

Line 218-219, 275: **“The long-term testing should cover at least 12 months’ duration at the time of submission.”**

It is recognized that this requirement is taken directly from ICH Q1A, however for some products long-term testing covering 12 months’ duration at the time of submission is too long. Many products have short shelf lives and can be technically defended with less than 12 months of data. Therefore, it is requested that submission be allowed when there is sufficient long-term testing that will support the requested expiration dating period.

Also, for products that are not new molecular entities (NMEs), 6 months of long-term data may be acceptable, e.g. amino acid solutions, LVP multi-chamber products, or combination products. Water Vapor Transmission Rate characterization of products in semi-permeable containers is very reliable with 6 months of data.

Lines 227-229: **“The first three production batches manufactured post approval, if not submitted in the original application, should be placed on accelerated and long-term stability studies using the same stability protocols as in the approved drug application.”**

Reduced testing for first production batches and/or annual stability batches should also be considered based on the data presented in the submission, and the application of good scientific principles as they relate to the stability and expiration dating of the product(s) covered by the submission. (See comments lines 2992-3004).

Lines 277-278 **“Where *significant change* occurs due to accelerated testing, additional testing at the intermediate condition (e.g., 30°C ± 2°C/60% ± RH 5%) should be conducted.”**

This section should allow for the use of an Arrhenius model to assist in predicting if an intermediate condition, e.g. 30°C would be acceptable. If the model indicates that an intermediate condition is expected to fail, additional testing should not need to be performed.

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Line 280: **“1. A 5 percent potency loss from the initial assay value of a batch.”**

It is recognized that the definition of significant change is taken directly from ICH Q1A, however, a 5% potency loss from the initial assay value is too restrictive. It is requested that this Guidance allow potency changes of greater than $\pm 5\%$, when justified, and provided there are no safety concerns, e.g. compendial products where the potency specification is greater than $\pm 5\%$. Additionally, analytical variation for some NDA products such as heparin, may complicate the ability to use a 5% criterion.

Line 286-288: **“Should significant change occur at 40°C/75% RH, the initial application should include a minimum of 6 months’ data from an ongoing 1-year study at 30°C/60 percent RH; the same significant change criteria shall then apply. [ICH Q1A].”**

This section should allow for the use of an Arrhenius model to assist in predicting if an intermediate condition, e.g. 30°C would be acceptable. If the model indicates that an intermediate condition is expected to fail, additional testing should not need to be performed.

Lines 298-301: **“In such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant, shorter expiration dating period, refrigerator temperature storage, more protective container and/or closure, modification to the formulation and/or manufacturing process should be considered during drug development.”**

In addition to the alternate approaches listed, the use of wider limits, with justification, should also be an option when considering alternate approaches.

Lines 305-306: **“The further accumulated data should be submitted to the FDA during the assessment period of the drug application. [ICH Q1A].”**

It is recommended that the data should be submitted to FDA upon request during the assessment or with the first annual report. It does not make sense to amend the file, to incorporate new data, after each

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testing period if the file is not under active review. Submitting data upon request minimizes the amendments yet provides the FDA with the timely and necessary information to conduct a thorough review.

Lines 309-310: **“A minimum of 4 test stations (e.g., 0, 2, 4, 6 months) are recommended for the 6 month accelerated stability study.”**

The test stations listed should not be the required test stations for a 6 month accelerated stability study, but rather an example of one of the possibilities. In some cases test stations at 0, 1, 3, and 6 months may be preferred. For instance, a 3 month test station is more appropriate for semi-permeable container systems.

Lines 326-329: **“• Accelerated condition: 40°C ± 2°C/15% RH ± 5% (hereafter referred to as 40°C/15% RH) [ICH Q1A];”**
“• Intermediate condition: 30°C ± 2°C/40% RH ± 5% (hereafter referred to as 30°C/40% RH);”
“• Long-term condition: 25°C ± 2°C/40% RH ± 5%”

SEE GENERAL COMMENTS, Storage Conditions for Drug Products in Semi-Permeable and Permeable Containers.

Lines 330-331: **“For liquids in glass bottles, vials, or sealed glass ampules, which provide an impermeable barrier to water loss,”**

Also included in this section as a container/closure system that provides an impermeable barrier to water loss is a semi-permeable container in a foil overpouch. A suggested rewording of these lines would be: “For liquids and solids packaged in containers designed to provide a permanent barrier to water loss (i.e., glass bottles, glass vials, sealed glass ampules, and semi-permeable containers in foil overpouches)”.

Line 353-354: **“A minimum of 4 test stations (e.g., 0, 2, 4, 6 months) are recommended for the 6 month accelerated stability study.”**

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The test stations listed should not be the only recommended test stations for a 6 month accelerated stability study, rather an example of one of the possibilities. In some cases test stations at 0, 1, 3, and 6 months may be preferred. For instance, a 3 month test station is more appropriate for semi-permeable container systems based upon the requirements proposal based upon the requirements proposed. See GENERAL COMMENTS, Storage Conditions for Drug Products in Semi-Permeable and Permeable Containers.

Lines 356-521: **“8. Application of ICH Stability Study Storage Conditions to Approved Applications”**

It is recommended that this section be placed in an addendum to the Guidance in order to provide better organization to the document.

Line 589-591: **“For sterile water for injection (WFI) and LVP solutions of inorganic salts packaged in semi-permeable containers (e.g., plastic bags) the following statement may be used on the immediate container labels:”**

It is recommended that SVP products of the same type be added where the same parameter (i.e. water loss from the container system) determines product shelf life. Some SVP products are covered in the same package insert as LVPs of the same type.

Lines 596-600: **“Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] Brief exposure to temperatures up to 40°C/104°F may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F) However such exposure should be minimized.”**

The labeling approach recommended with regard to brief exposure to higher temperatures and mean kinetic temperature is acceptable. It is suggested, however, that the portion of statement related to mean kinetic temperature (Line 599) be modified to provide additional clarity for pharmacists and other users by restating mean kinetic temperature as “average or mean kinetic temperature”.

Line 643-648: **“Table 2: Summary of Uniform Storage Statements in Drug Product Labeling”**

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Typographical Errors in Table 2

Change from: "Store at 25°C (77°F)" to "Store at 25°C (77°F)"
Change from: "Store at 25/C (77°F)" to "Store at 25°C (77°F)"

SEE ALSO GENERAL COMMENTS, Storage Statements.

Line 656:

Typographical Error in Table 3

For column titled, "LVP in a plastic bag . . .",

Change from: "25°C±2°C/60%RH±5%" to: "25°C±2°C/40%RH±5%"

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Lines 667-670: **“For applications approved prior to the publication of this guidance, the recommended storage statements should be adopted through the annual report mechanism at the next printing opportunity if desired, but within three years of the date of the final guidance.”**

It is requested that five years be allowed for the adoption of the storage statements. Five years is a more reasonable time frame based on the potential impact and logistics involved in a label conversion for hundreds of product formulations.

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SECTION III: STABILITY TESTING FOR ABBREVIATED NEW DRUG APPLICATIONS

Lines 736-738: **“• Additional stability studies (12 months at the intermediate conditions, or long-term data through the proposed expiration date) if significant change is seen after 3 months during the accelerated stability study.”**

Requiring 12 months of stability data at the intermediate condition, if a significant change is seen after 3 months at an accelerated condition is inappropriate because it is more stringent than the requirements set for NDAs where 6 months of data at 30°C are required where warranted.

Line 756-759 **“Additional stability studies (12 months at the intermediate conditions or long-term stability testing through the proposed expiration date) if significant change is seen after 3 months during the accelerated stability studies (the tentative expiration dating period will be determined based on the available data from the additional studies.”**

Requiring 12 months of stability data at the intermediate condition, if a significant change is seen after 3 months at an accelerated condition is inappropriate because it is more stringent than the requirements set for NDAs.

Lines 767-768: **“If formulated with an overage, the overage should be justified as necessary to match that of the referenced drug.”**

Justification of a formulation overage by matching to the reference drug may not be possible because, in many cases, the formulation of the reference drug may be proprietary and no information would be available. Formulation with an overage should be allowed, if justified.

Lines 779-782: **“Extension of the tentative expiration dating period should be based on data generated on at least three production batches tested according to the approved protocol outlined in the stability commitment.”**

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Since the approved tentative dating is based on the stability data and the analysis of that data, extension of dating should also be acceptable (if supported by the data) based on those same studies. The following is suggested: "If the stability studies on the batches included in the regulatory application are continued after the approval, it is feasible to extend the tentative expiration dating period based on full long-term data obtained from these batches in accordance with the approved protocol, including statistical analysis if appropriate, provided the studies to be used for the dating extension are clearly identified in the submission. However, the expiration dating period thus derived remains tentative until confirmed with full long-term data from at least three production batches." (See comments lines 1467-1472).

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SECTION IV: STABILITY TESTING FOR INVESTIGATIONAL NEW DRUG APPLICATIONS

Lines 836-837: **“In stability testing during phase 3 IND studies, the emphasis should be on testing final formulations in their proposed market packaging and manufacturing site based on the recommendations and objectives of this guidance.”**

It is recommended that, “and manufacturing site” be deleted since it may not be possible to manufacture these batches at the final intended commercial manufacturing site. SEE ALSO GENERAL COMMENTS, Site Specific Stability.

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SECTION V: APPROVED STABILITY PROTOCOL

Line 859-860: **“The stability protocol should include methodology for each parameter assessed during the stability evaluation of the drug substance and the drug product.”**

It should not be necessary to include methodology in each protocol if the information is already available in an approved submission. A reference to the methodology should be acceptable, considering it would allow for a more concise protocol. Therefore, the following statement is recommended to replace that existing on lines 859-860: “The stability protocol should include methodology or a reference to the methodology for each parameter assessed during the stability evaluation of the drug substance and the drug product”.

Lines 862-864: **“The stability indicating methodology should be validated by the manufacturer and described in sufficient detail to permit validation and/or verification by FDA laboratories.”**

The methodology may be validated by an outside laboratory, with the appropriate transfer to the testing sites. It is suggested that “by the manufacturer” be deleted from the statement.

Line 867-869: **“For the drug product, the protocol should support a labeling storage statement at CRT, refrigerator temperature, or freezer temperature.”**

Regardless of the storage conditions, the protocol must support the labeled storage statement, and Section II.A.4 and II.B.5 discuss storage condition requirements. Therefore, a reference to specific storage conditions isn't necessary in this section and the above statement could be modified to read: “For the drug product, the protocol should support the labeled storage statement”.

Lines 896-900: **“A stability commitment is acceptable when there are sufficient supporting data to predict a favorable outcome with a high degree of confidence, such as when an application is approved with stability data available from pilot-plant batches, when a**

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supplement is approved with data that do not cover the full expiration dating period, or as a condition of approval.”

The following modification is recommended as being more consistent with the 1987 Stability Guideline document: “A commitment to obtain data is acceptable in lieu of stability data when there are sufficient supporting data to predict a favorable outcome with a high degree of confidence, such as when an application is approved with stability data available from pilot-plant batches, or when a supplement is approved with data that do not cover the full expiration dating period.”

Lines 905-906: **“Submit stability study results at the time intervals and in the format specified by the FDA, including the annual batches.”**

Since Section VI of this Guidance document defines the reporting requirements, it is recommended that this section be modified to state, “submit updated study results for ongoing and committed studies.” The placement of reporting requirements in one section of the Guidance document would allow for establishing more consistent requirements across the entire Guidance document.

Lines 919-926: **“The approved stability protocol should be revised as necessary to reflect updates to USP monographs or the current state-of-the-art regarding the types of parameters monitored, acceptance criteria of such parameters, and the test methodology used to assess such parameters. However, other modifications are discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches. Once a sufficient database is established from several production batches to confirm the originally approved expiration dating period, it may be appropriate to modify the stability protocol. See Section IX.J.”**

The phrase “state-of-the art” seems vague. It is unclear what type of changes are envisioned as “current state-of-the-art”.

Also, reduced testing for first production batches and/or annual stability batches should be considered based on the data presented in the submission, and the application of good scientific principles as

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they relate to the stability and expiration dating of the product(s) covered by the submission. (See comments lines 2992-3004).

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SECTION VI: REPORTING STABILITY DATA

The amount of information requested for a single report appears excessive and/or repetitive to that presented in the protocol. A report containing all of the required information would make the report complex and interpretation confusing. Much of the requested information can be easily determined by simple analysis of the presented data (e.g., standard deviation). Also, the inclusion of too much information would detract from the important content in the report while adding little additional value.

Although report formatting is important in order to present the data in a concise manner, it seems that if stability results are reported on a timely basis and meet the general criteria for reporting, then format should not be an issue. There are currently several different formats in use in the Pharmaceutical industry, and different product types might better lend themselves to varying formats in order to more clearly and concisely present the information. Therefore, it is suggested that alternate reports formats be considered.

Line 982: **“The following data analysis of quantitative parameters should be provided:”**

This statement suggests that an analysis of all quantitative parameters should be conducted. The analysis of only appropriate or shelf-life limiting parameters should be required since it is only the unstable constituents that limit a product’s shelf-life.

Line 989-990: **“Regulatory specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted).”**

This requirement is inconsistent with the ICH Q6A document which allows for “in-house” limits for release and regulatory specifications for the full expiration dating period.

Lines 1005-1048: **“Table 4: Model Stability Data Presentation”**

Table 4 provides a nice description of the FDA expectations with regard to format, but it seems that the table requires too much information that must be gathered from too many sources. The table would be more useful if only the applicable parameters were reported.

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Also, clarification of "Sampling Plan" is requested since it is unclear what the expectation is, from a data presentation standpoint.

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SECTION VII: SPECIFIC STABILITY TOPICS

Lines 1050-1126: **“A. Mean Kinetic Temperature”**

SEE GENERAL COMMENTS, Mean Kinetic Temperature

Lines 1127-1187 **“B. Container/Closure”**

Lines 1167-1169: **“Upright versus inverted/on-the-side stability studies should be performed during the preapproval and post approval verification stages of the stability program.”**

If justification of a worse case position can be determined, it should only be necessary to conduct future studies in the most stressful orientation.

Line 1174: **“Specific extractables testing on a drug product is not recommended.”**

It is agreed that extractables testing is not necessary on the drug product since this parameter should be evaluated as part of container system as discussed in VII.B.

Lines 1178-1181: **“Such testing should demonstrate that the levels of extractables found during extraction studies, which are generally performed with various solvents, elevated temperatures and prolonged extraction times, are at levels determined to be acceptable, and that those levels will not be approached during the shelf life of the drug product.”**

The comment “levels will not be approached” is vague. If studies have been conducted to characterize, evaluate, and understand container extractables, then the only requirement should be that extractable levels should not exceed the defined levels.

Lines 1182-1184: **“Loss of active drug substance or critical excipients of the drug product by interaction with the container/closure components or**

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components of the drug delivery device is generally evaluated as part of the stability protocol.”

It is inappropriate to evaluate the interaction of container/closure components or components of the drug delivery device with parenteral drug products since the number of product codes and components and/or device system combinations available in the market is quite large. This would represent an enormous financial burden for pharmaceutical companies.

Lines 1188-1248: **“C. Microbial Control and Quality”**

Lines 1223-1236: **“3. Sterility Assurance of Sterile Drug Products”**

“The stability studies for sterile drug products should include data from a sterility test of each batch at the beginning of the test period. Additional testing is recommended to demonstrate maintenance of the integrity of the microbial barrier provided by the container and closure system. These tests should be performed annually and at expiry.

Integrity of the microbial barrier should be assessed using an appropriately sensitive and adequately validated container and closure integrity test. The sensitivity of this test should be established and documented to show the amount of leakage necessary to detect a failed barrier in a container and closure system. The number of samples to be tested should be similar to the sampling requirement provided in current USP ‘Sterility Tests’ <71>. The samples that pass container and closure integrity testing may be used for other stability testing for that specific time point, but should not be returned to storage for future stability testing. Container and closure integrity tests do not replace the current USP ‘Sterility Tests’ <71> or 21 CFR 610.12 for product release.”

For products where parametric release criteria are used for batch release, meeting the release criteria may serve in place of a sterility test at the beginning of the test period.

Since the purpose of the USP sterility test performed as part of a stability study is “to demonstrate maintenance of the integrity of the microbial barrier provided by the container and closure system”, requiring a routine microbial ingress test as part of these studies is redundant. It is recommended that the paragraph related to microbial

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ingress testing be amended as follows: “Alternately, integrity of the microbial barrier may be assessed using an appropriately sensitive and adequately validated container and closure integrity test. The sensitivity of this test should be established and documented to show the amount of leakage necessary to detect a failed barrier in a container and closure system. The number of samples to be tested should minimally meet the sampling requirement provided in current USP ‘Sterility Tests’ <71>. The samples that pass container and closure integrity testing may be used for other stability testing for that specific time point (if appropriate), but should not be returned to storage for future stability testing. Container and closure integrity tests do not replace the current USP ‘Sterility Tests’ <71> or 21 CFR 610.12 for product release.”

Lines 1237-1248

“4. Pyrogens and Bacterial Endotoxins”

We do not believe that there is any value in testing for pyrogens or bacterial endotoxins during a stability study for a sterile solution product. Pyrogen or bacterial endotoxins testing of sterile products at the initiation of the stability test period is necessary to assure products entering stability testing have met all necessary release criteria. However, this draft guidance goes on to say that “Products containing liquids in glass containers with flexible seals or in plastic containers should be tested no less than at the end of the stability test period.” (lines 1243-1244) It is unclear why it should be necessary to test sterile solution products at the end of the stability test period if the product originally passed pyrogens or bacterial endotoxins at the beginning of the stability test period.

Sterile parenteral solutions that initially pass pyrogen or bacterial endotoxin release testing cannot become re-contaminated with pyrogens or bacterial endotoxins unless live microorganisms are able to infiltrate the solution containers and grow and multiply therein.

Based on the information presented in this section it must be concluded that pyrogen or bacterial endotoxins tests performed at the end of the stability test period are being used as indirect tests for assessing container/closure integrity. Parenteral solutions, however, have already undergone direct testing to assure solution container/closure integrity. It may be possible for containers to become cracked or damaged, and thereby to become breached by microbes, but the same problem could occur with sterile parenterals in

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glass ampules, which this Guidance indicates does not need to be tested for pyrogens or endotoxins at the end of their stability test period.

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Lines 1346-1447: **“E. Statistical Considerations and Evaluation”**

Lines 1348-1367: **“1. Data Analysis and Interpretation for Long-term Studies”**

Statistical analyses may be a powerful tool in evaluating stability data and providing a high level of confidence with respect to product meeting specifications throughout the expiration dating period. This section describes only one acceptable statistical approach for expiration dating. Statistical procedures which are equally acceptable and should be allowed without prior agency approval.

Lines 1356-1358: **“The methods described in this section are used to establish with a high degree of confidence an expiration dating period during which average drug product attributes such as assay and degradation products of the batch will remain within specifications.”**

This section describes only one acceptable statistical approach for expiration dating. There are other statistical approaches available for the evaluation of stability data, which are equally acceptable, and that in some cases are more appropriate for the evaluation of this type of data. It is recommended that a statement be added to allow for use of alternate appropriate statistical approaches.

Lines 1365-1367: **“Applicants wishing to use a statistical procedure other than those discussed in this guidance should consult with the chemistry review team prior to initiation of the stability study and data analysis.”**

It is recommended that this statement be modified as follows to not require consult with the chemistry review team prior to initiation, given that final judgment regarding the acceptability rests with the Agency review team. **“Alternate statistical approaches may be used as appropriate to evaluate stability data for the purpose of establishing expiration dating. These approaches must provide the same high degree of confidence that the average drug product attributes will remain within specifications throughout the expiration dating period.”**

Line 1414: **“The level o significance . . .”**

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Typographical error: Should read “The level of significance . . .”

Line 1416: **“A p-value of 0.25 for preliminary statistical tests has been recommended.”**

This section should more clearly indicate that a p-value of 0.25 is just an example, and that other values for the level of significance of rejection may be appropriate.

Lines 1418-1420: **“If these tests resulted in p-values less than 0.25, a judgment should be made as to whether pooling could be permitted. The appropriate FDA chemistry review team should be consulted regarding this determination.”**

It is recommended that this statement be modified as follows to not require consult with the chemistry review team, given that final judgment regarding the acceptability rests with the Agency review team. “If these tests resulted in p-values less than 0.25, and data are pooled, the final judgment on whether pooling should be permitted lies with the Chemistry review team.”

Lines-1448-1532: **“F. Expiration Dating Period/Retest Period”**

Lines 1456-1458: **“In general, proper statistical analysis of long-term stability data collected, as recommended in Section VII.E. and exemplified in Figure 1, should support at least a one-year expiration dating period. Exceptions do exist, for example, with short half-life radioactive drug products.”**

It is recommended that these statements be deleted. While it is agreed that many pharmaceutical products have expiration dating periods in excess of one year, these dating periods are due to the stability of the product, and not to a proper statistical analysis. There are many acceptable products with expiration dating periods of less than one year that are supported by the appropriate statistical analysis.

Lines 1467-1472: **“Alternately, if the stability study on at least three pilot-scale batches is continued after the NDA/BLA approval, it is feasible to**

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extend the tentative expiration dating period based on full long-term data obtained from these batches in accordance with the approved protocol, including statistical analysis if appropriate, through a prior approval supplement. However, the expiration dating period thus derived remains tentative until confirmed with full long-term data from at least three production batches.”

Under 21 CFR 314.70(d)(5), a new drug applicant may take certain actions on the basis of an approved stability study protocol, such as extending an expiration dating period based on full shelf-life data without prior approval of a supplemental application by including the change in the next annual report under 314.81(b)(2). The statement as written requires the preapproval supplement for extension of dating, even though there is an approved protocol. It appears, based on the statement in lines 1464-1466, that the concern is the studies used to support the dating extension. It is therefore recommended that the statement be modified as follows: “Alternately, if the stability studies on the batches included in the regulatory application are continued after the NDA/BLA approval, it is feasible to extend the tentative expiration dating period based on full long-term data obtained from these batches in accordance with the approved protocol, including statistical analysis if appropriate, provided the studies to be used for the dating extension are clearly identified in the submission. However, the expiration dating period thus derived remains tentative until confirmed with full long-term data from at least three production batches.”

Lines 1480-1489: **“b. Shortening of Expiration Dating Period”**

The shortening of a product’s expiration date could result from a precautionary reduction in dating or a permanent reduction based on the analysis of stability data. In some cases, as a precautionary measure expiration dating may be temporarily reduced. If the reduction is meant to be temporary then there should be no need to reapply for extended dating. In the case where stability data support a reduction in dating then the additional studies with a CBE Supplement would be required to extend dating.

Lines 1483-1484: **“The expiration dating period should be shortened to the nearest available real-time long-term test point where the product meets acceptance criteria.”**

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Since the expiration dating period is based on statistical evaluation of the data, it is recommended that the statement be modified as follows to allow for appropriate use of statistical analysis. "The expiration dating period should be shortened to the nearest available real-time long-term test point where the product meets acceptance criteria, or to a period supported by statistical analysis of the available stability data."

Lines 1533-1637: **"G. Bracketing"**

Lines 1594-1595: **"A bracketing design that is not contained in the approved protocol in the application is subject to supplemental approval (21 CFR 314.70(b)(2)(ix)) (601.12)."**

This requirement is unnecessarily restrictive in that product stability has been previously established during product development. It is suggested that the alternate procedure, described in line 1599-1603, should be the primary source for approval.

Lines 1638-1821: **"H. Matrixing"**

Lines 1670-1672: **"Factors that should not be matrixed include initial and final time points."**

The Regulatory concept of testing at initial and final time points is valid, but the statement is unnecessarily restrictive because it does not allow for other methods, (e.g., response surface methodology). The matrixing option should not be ruled out if it can be justified.

Lines 1704: **"Same as Section VII.G.1.c"**

Typographical error. Line should read: "Same as Section VII.G.2.c."

Lines 1717-1720: **"All samples should be placed on stability including those that are not to be tested under the matrixing design. Once the study begins, the protocol should be followed without deviation. The only exception is that, if necessary, it is acceptable to revert back to full stability testing during the study. But once reverted, the full testing should be carried out through expiry."**

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There should be flexibility in when, how much, and for how long full stability testing may be required in a matrix design. Allowances should be made for reverting to full stability testing on an interval by interval basis in order to perform a technical assessment of test results. This assessment may or may not dictate full stability testing at all future intervals. Additionally, allowances should be provided for full testing of specific parameters only, e.g. problematic assays, tests that would be important in determining the shelf life of the product, while testing of stable constituents that are not predictors of product stability would be superfluous.

Lines 1721-1742: **“b. Size of matrixing design”**

The matrixing of stability studies can be very beneficial, but the guidelines as currently described, are too strictly defined. The requirements are restrictive in that the design of matrices is based on the “number of combination of factors and the amount of supportive data available”. Additional flexibility in matrix design is requested and should be also based on scientific principles and not only the amount of supportive data available .

Several statistical approaches to matrix design are appropriate, and the approach described in lines 1736-1742 should be used as an example. The approach described in this section should be identified as an example of one of many possible approaches, rather than a specific approach, since there are other acceptable methods of matrix design.

Lines 1893-1894: **“b Additional long-term stability data and, if applicable, accelerated data should be submitted for review as soon as they become available prior to the approval.”**

It is recommended that the data be submitted to FDA upon request during the assessment, or with the first annual report. Submitting data upon request minimizes the amendments yet provides the FDA with timely and necessary information to conduct a thorough review.

Lines 1823-1950: **“Section I. Site Specific Stability Data for Drug and Biologic Applications”**

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SEE GENERAL COMMENTS, Site Specific Stability Data

Lines 1946-1947: **“Drug substance batches used to produce site-specific drug product batches should be clearly identified. Additional long-term stability data and, if applicable, accelerated data should be submitted for review as soon as they become available prior to the approval.”**

The requirement to identify drug substance batches is clearly identified as information required in the data package, and is redundant here. It is recommended that the data be submitted to FDA upon request during the assessment, or with the first annual report. Submitting data upon request minimizes the amendments yet provides the FDA with timely and necessary information to conduct a thorough review.

Lines 2227-2241: **“Section K. Degradation Products”**

This section appears to describe requirements related to activities that should have been completed prior to stability studies, and therefore the requirements of this section may be better placed in a more appropriate guidance document with only a reference to that document appearing in this section.

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SECTION VIII: CONSIDERATIONS FOR SPECIFIC DOSAGE FORMS

Lines 2685-2695 **“M Large Volume Parenteral (LVPs)”**

Lines 2686-2687: **“Evaluation of LVPs should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, pyrogenicity, clarity, and volume.”**

We do not believe that there is any value in testing for pyrogenicity during stability (see comments lines 1237-1248), and it is recommended this test be deleted from the list of recommended evaluations.

Also, weight loss evaluations should be an acceptable alternative to volume.

Lines 2693-2695: **“Interaction of administration sets and dispensing devices with this type of dosage form should also be considered through appropriate use test protocols to ensure that absorption and adsorption during dwell time do not occur.”**

It is inappropriate to evaluate the interaction of administration sets and dispensing devices with LVPs since the number of product codes and device system combinations available in the market is quite large. This would represent an enormous financial burden for pharmaceutical companies.

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SECTION IX: STABILITY TESTING FOR POST-APPROVAL CHANGES

Lines 2732-2765: **“A. General”**

This section, as written, in general addresses requirements for those products for which separate Guidance documents have been written addressing stability (as well as other requirements) for post approval changes. It is recommended that some minimum recommendations be included here for those products not covered by separate Guidance documents (even if only consistent with the 1987 Guideline for Stability), until replaced with other guidance documents.

Recommendations for Sterile Aqueous Products are being provided considering the existing SUPAC recommendations and what is considered to be scientifically appropriate for these types of products:

Lines 2792-2808: **“C. 1 Site Change for the Drug Substance”**

A Type 1 stability data package submitted with a CBE supplement.

Lines 2809-2825 **“C.2 Drug Product Manufacturing Site Changes”**

SEE GENERAL COMMENTS, Site Specific Stability Data

Lines 2826-2836: **“C.3 Change in Packaging Site”**

A Type 0 stability data package submitted with a CBE supplement is recommended.

Lines 2837-2852: **“C.4 Change in Testing Laboratory”**

A Type 0 stability data package submitted with a CBE supplement is recommended.

Lines 2853-2871: **“D. Formulation Changes”**

For a change in the source of active (same grade, meets same specifications) a Type 1 stability data package submitted with a CBE

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(if supplier has FDA approval) or PA supplement (if supplier does not have FDA approval) is recommended.

Changes in the source of inactive or excipients (same grade, meets same specifications) a Type 0 stability data package submitted with the AR would be required.

For a change in the grade of active material a Type 2 (comparative) stability data package with a PA supplement would be required.

For a change in grade of the inactive or excipient a Type 1 (comparative) stability data package with a PA supplement is recommended.

Lines 2872-2896: **“E. Addition of a New Strength”**

If the new strength is bracketed in concentration by existing products a Type 1 stability data package with a PA supplement is recommended.

If the new strength is not bracketed in concentration by existing products a Type 2 stability data package with a PA supplement would be necessary.

Lines 2897-2925: **“F. Change in Manufacturing Process and/or Equipment”**

For changes to the process within the allowable processing ranges, changes from non-automated to automated equipment, or changes to alternate equipment of the same design and operating principles, a Type 0 stability data package is recommended.

For changes outside the allowable processing ranges or for equipment of different design or operating principles a Type 1 stability data package with a CBE supplement would be necessary.

For a change in the type of process (for example a change from aseptic fill to terminal sterilization) a Type 2 (comparative) stability data package with a PA supplement would be required.

For a change in the source of active (same grade, meets same specifications) a Type 1 stability data package submitted with a CBE

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An increase in the batch size beyond 10 times the batch size of the clinical/stability batches a CBE with Type 2 stability data at time of submission is recommended, but not additional stability commitments beyond the regular annual batches.

Lines 2944-2955: **“H. Reprocessing of a Drug Product”**

The reprocessing of a drug product would require a Type 2 (comparative) stability data package with a PA supplement. Post approval commitments for reprocessed product should not be required if the data package demonstrate no impact on the stability profile of the product.

Lines 2956-2991: **“I. Change in Container and Closure”**

For changes to non solution contact materials, i.e. changes that do not affect the protective properties of the container/closure system, a Type 0 stability data package is recommended.

Changes to non solution contact materials that affect the protective properties of the container/closure system, a Type 2 (comparative) stability data package is recommended.

Changing size of the container/closure within the approved range of sizes would necessitate a Type 0 stability data package.

Changing size of the container/closure outside the approved range of sizes would require a Type 2 stability data package

For changes to solution contact materials a Type 2 (comparative) stability data package is needed.

Lines 2992-3004: **“J. Changes in Stability Protocol”**

This section indicates that reduction in testing is discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches, and that this change in the protocol will require a PA supplement. A request for reduced testing for first production batches and/or annual stability batches should also be considered based on the data presented in the

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submission, and the application of good scientific principles as they relate to the stability and expiration dating of the product(s) covered by the submission.

Lines 3010-3012: **“It should be noted, however, that the reduced testing protocol applies only to annual batches and does not apply to batches used to support a post approval change that requires long-term stability data at submission and/or as a commitment.”**

The original approved protocol is not always the most appropriate protocol for the evaluation of product changes. It is requested that this section be modified to allow for using a protocol other than the original approved protocol for evaluation of product changes (with submission of the protocol with the data), and for a provision of consulting with the agency through general correspondence regarding the proposed protocols.

Lines 3013-3014: **“Furthermore whenever product stability failures occur, the original full protocol should be reinstated for annual batches until problems are corrected.”**

Simply reinstating the full original protocol for annual batches may result in additional testing, but insufficient, or even inappropriate data to characterize changes to the stability profile and provide the appropriate level of confidence in the product expiration dating. The following change is recommended. “When a product stability failure occurs an investigation should be conducted. Based on the outcome of the investigation an action plan should be developed. The product expiration dating period should be adjusted if appropriate, and modified stability protocols designed to adequately characterize any changes to the product, and provide assurance with respect to meeting expiration dating should be developed. The modified protocols should be submitted in a CBE supplement, with notification of the reduced dating.”

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Listing of Attachments

1. Copy of 7/15/99 comments regarding Site Specific Stability
2. Copy of 8/24/98 HIMA Technical Position Paper sent to Dr. Roger Williams
3. Copy of 3/1/99 correspondence from Dr. J. Curley

**Draft Guidance for Industry
Stability Testing of Drug Substances and Drug Products
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Attachment 1

Copy of 7/15/99 Comments regarding Site Specific Stability



July 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Rm 1-23
Rockville, MD 20857

**Re: DOCKET NUMBER: 98D 0362
Site Specific Stability Data for Drugs and Biologic Applications**

Dear Madam or Sir:

The enclosed information is being submitted on behalf of the HIMA Large Volume Parenteral (LVP) Task Force in response to the Agency's request (at the March 31, 1999 Open Meeting) for information and/or data supporting industry's position regarding FDA's Revised Draft Proposal on Site Specific Stability Data.

Technology transfer and process validation studies demonstrate conformance to cGMP, support the reproducibility and robustness of the process, and provide assurance that the drug products will meet established specifications. If the specifications are met, and the manufacturing process is shown to be equivalent, there is no technical basis to support the need for product stability data. Data for reviewed site transfers approved from 1980 to present indicate there are no related stability failures of sterile parenteral products. The following summarize the affected regulatory files and products:

Summary of Products Reviewed

Number of Regulatory Files	61
Number of Products Affected	123
Types of Products	SVP's, Premix Drugs, Amino Acid Injections, and LVPs

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Marlene Tandy to Dockets Management Branch (HFA-305)

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Dated July 15, 1999

HIMA believes that these data support the position presented at the March 31, 1999 Open meeting, i.e. that our experience base has not identified any difference in product stability due to manufacturing site change alone. HIMA recognizes that these data represent sterile solution products, and that the Agency must consider all types of product in the guidance. In the event the data presented do not support a similar position for all types of products, it is recommended that the Agency's Revised Proposal for Site Specific Stability be modified to include Sterile Solution Products in the 'Minor' rather than 'Moderate' category with respect to potential to have an adverse effect on product stability due to a site transfer.

We appreciate the opportunity to comment. If you have any questions regarding our comments, please contact me.

Sincerely,

A handwritten signature in cursive script that reads "Marlene Tandy" followed by a stylized monogram.

Marlene Tandy, M.D., J.D.

HIMA

(202) 783-8700

(202) 783-8750 (Fax)

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Attachment 2

Copy of 8/24/98 HIMA Technical Position Paper sent to Dr. Roger Williams



August 24, 1998

Roger Williams, M.D.
Deputy Center Director for Pharmaceutical Science, Rm 6027
Office of Pharmaceutical Science, WOC2
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

and

PhRMA Stability Technical Working Group
c/o Mr. Thomas White, Associate Vice President
PhRMA
1100 Fifteenth Street, NW
Washington, DC 20005

**RE: ICH Requirements for Solutions in Semi-Permeable Containers
Technical Position Paper**

Dear Dr. Williams and Mr. White:

The HIMA Large Volume Parenteral (LVP) Systems Task Force has prepared a technical position paper regarding stability conditions for solution products in semi-permeable plastic containers. Much of the information contained in the paper has been previously reported in other correspondence. The task force continues to be very concerned about this topic and understands it may be discussed in ICH working group discussions scheduled for next week in Japan. On behalf of the task force, I am submitting this paper with our recommendations regarding stability conditions for consideration. We are also forwarding this information to PhRMA's stability technical working group. Task force member firms are not members of PhRMA and have no direct means for participating in the ICH discussions. We appreciate the opportunity to provide this information to PhRMA and the Agency and suggest that you share the information with regulator and industry colleagues from Europe and Japan.

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We would be available to discuss any comments that may arise, or to provide additional information that may be helpful. You may contact me directly at (847)270-4637, or you may call Marlene Tandy, M.D., J.D. at HIMA on (202)434-7225.

We trust this information will be useful and look forward to further discussion on this topic.

Sincerely,



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**Harmonized Stability Conditions for Solutions
in Semi-Permeable Plastic Containers**

Technical Position Paper

HIMA LVP Systems Task Force

August 24, 1998

I. Background

The HIMA LVP Systems Task Force has had an ongoing dialogue with the Food and Drug Administration regarding stability conditions for parenteral solutions in semi-permeable, plastic container systems. For a number of years, these discussions were primarily focused on appropriate conditions for the United States. More recently, however, discussions have broadened beyond U.S. considerations as this has become a specific topic within the ICH technical working group.

The task force membership is comprised of multiple U.S. manufacturers of parenteral solutions in large (LVP) and small (SVP) volume containers. Some members also manufacture and market solutions in plastic containers in other regions of the world, including Europe and Japan. Task force member firms are not members of PhRMA and have had no direct means to participate in ICH discussions.

The task force appreciates the complexity involved in developing harmonized technical and regulatory requirements and recognizes the significant efforts and accomplishments from all parties in the finalization of the existing Q1A document on stability. We also understand the value that harmonization can bring by enabling a single set of studies to support product registration and commercialization in all three regions.

Our review of the development of the Q1A document indicates that the primary technical considerations were associated with solid, oral dosage forms. This approach is consistent with the majority of new product applications which are for solid dosage forms. The existing Q1A document contains minimal specific guidance for solutions in semi-permeable containers. The only reference to such dosage forms recommends consideration be given to low relative humidity conditions since such conditions can adversely affect these products. The specific example cited is 10-20% relative humidity. It has been presumed this consideration applies to accelerated testing.

We believe considerations specific to parenteral dosage forms in semi-permeable containers should form the basis for developing more detailed recommendations for

harmonized technical and regulatory requirements. This paper summarizes the task force position on this topic. We request all regulator and industry parties involved in ICH discussions consider this information. We are willing to provide additional information or clarification.

II. Recommended Storage Test Conditions

- Long Term Testing: $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ /Not more than $60\% \pm 5\%$ Relative Humidity with 6 months data at time of submission. For products also intended for the U.S. region use of a lower relative humidity is appropriate, i.e., 40%.

Expanded information regarding recommendation presented in Section V.

- Accelerated Testing: $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ /Not more than $60\% \pm 5\%$ Relative Humidity with 6 months data at time of submission. For products also intended for the U.S. region use of a lower relative humidity is appropriate, i.e., 15% where significant change due to water loss effects is limited to a 3 month assessment.

Expanded information regarding recommendation presented in Section VI.

- Intermediate Testing: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ /Not more than $60\% \pm 5\%$ Relative Humidity with 6 months data from a 12 month study at time of submission. For products also intended for the U.S. region use of a lower relative humidity is appropriate, i.e., 40% where significant change due to water loss effects is limited to a 9 month assessment.

Expanded information regarding recommendation presented in Section V.

III. Key Points

Technical considerations which differentiate solutions in semi-permeable containers from solid dosage forms:

- Water loss from plastic container systems can play a major role in stability evaluations and expiration dating for solution products packaged in semi-permeable, plastic containers. Studies on such products have consistently demonstrated that moisture loss is the stability-limiting parameter for the majority of these products based upon the **upper** limits of concentration specifications. Water vapor transmission through the semi-permeable plastic containers is a physical, predictable phenomenon (not chemical degradation) dependent upon temperature, humidity and the inherent properties of the specific plastic container system used. Water loss is container-dependent over the typical concentration

ranges of the various solution solutes and is, therefore, independent of the specific drug solution. The effect of water loss is an increase in solute concentration, not solute loss associated with degradation. Thus, the implications of water loss and the selection of relative humidity conditions for stability testing is technically differentiated from solid dosage forms where the relative humidity testing conditions assess the potential for moisture-mediated chemical degradation.

- Since it is well established that steady-state water loss increases linearly with time under constant temperature and humidity conditions, water vapor transmission rates (WVTR) for specific container system configurations can be reliably characterized in less than 6 months of study.
- The effect of relative humidity on water loss is understood and predictable and, based upon Fick's Law, is directly proportional to the water vapor pressure differential inside the container system to that outside the container system. Lower water loss is observed at higher relative humidities. This can be contrasted to the effect of temperature on water loss rate which is container system dependent based upon the specific activation energy for water loss (more detailed information on water loss activation energies estimated for a variety of container system configurations is presented in Section VII).
- Expiration dating requirements and practices for solution products in plastic containers vary widely. In Japan, 3-year expiration dating is standard; in the U.S. 12- to 18-month dating is common.

The task force supports the development of harmonized stability requirements for solutions in semi-permeable containers **only** if:

- The long commercial track record which demonstrates a lack of stability/storage issues for these products is recognized and used as a basis for determining appropriate harmonized stability conditions.
- The required storage conditions do not unnecessarily become more stringent than they are today. Arbitrarily tightened requirements in any region would have an unwarranted and significant impact on product design, cost, user features and natural resources utilized, with no offsetting benefits, because some container systems in use today would not meet the proposed conditions. **This is a major issue due to how the QIA guideline has been implemented in the regions. Existing container systems should be suitable for use with new solutions involving new chemical entities or otherwise requiring new dossiers.**

Specifically, the task force does not support harmonized requirements such as:

- Long term testing at 40% relative humidity for products marketed only in Europe or Japan
- Accelerated testing for 6 months at 15% relative humidity
- Intermediate testing for 12 months at 40% relative humidity

We conclude that a single set of harmonized conditions for semi-permeable container systems is not practical. The proposed conditions allow the continued use of 60% relative humidity in Europe and Japan, and also meet FDA's preference for products within the U.S. We believe this approach is technically appropriate and defensible, clear, and durable to the practical aspects of guideline adoption in the various regions.

Additional detail in support of the recommended conditions and key points follows in the remaining sections:

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IV. Historical Considerations

It is worthwhile to note stability conditions with which task force firms have historical experience for solution filings in Europe, Japan, and the United States. These experiences and the most recent ICH proposal are summarized in **Table 1**.

Table 1.
Products in Semi-Permeable Containers
Historical Experience and Proposed Stability Conditions by Region

	Standard* ICH Conditions	European Experience	Japanese Experience	United States Experience	HIMA Task Force Proposal
Long Term	25°C 60% RH	25°C 60% RH	25°C 60% RH	25°C 40% RH	25°C 60% RH** 40% if also U.S.
Intermediate	30°C 60% RH 12 mo.**	Variable	Not Applicable	Not Applicable	30°C 60% RH 12 mo.** 40%/9 mo. if also U.S.**
Accelerated	40°C 75% RH 6 mo. (10-20% RH)***	40°C 60 - 75% 6 mo.	40°C 60 - 75% 6 mo.	40°C ≈15% RH 3 mo.	40°C 60% RH 6 mo. 15%/3 mo. if also U.S.
Typical Shelf Life	--	2-3 yr	3 yr	1-2 yr	--

* Temperature \pm 2°C; Relative Humidity \pm 5% RH.

** 6 month minimum time period at time of submission.

***Low relative humidity example for semi-permeable containers

V. Long Term and Intermediate Conditions

The task force believes that 60% RH is a more appropriate condition for a **harmonized** stability requirement at 25°C, as well as 30°C. Again, our position is that the long commercial track record, which demonstrates a lack of stability/storage issues for these products in all three regions, must be recognized in the development of harmonized standards. **The imposition of a 40%RH requirement in Europe and Japan has significant implications for products in those marketplaces today! Therefore, we question the value of international harmonization with a relative humidity of 40%RH.**

First, Japan has historically expected 3 years of acceptable stability under the long term conditions at 60% relative humidity. Based upon information presented in Section VI and VII below, a product designed for a 3-year water loss barrier at 25°C and 60% RH would not retain acceptable stability for longer than about 24 months at 40%RH.

Similarly, commercial products in Europe would also be impacted by the proposed conditions. In a European study of 16 product configurations, at least 2 of the configurations would not meet a minimum shelf-life with a 40% RH criterion.

Further, data presented by Grimm indicates that 60% relative humidity is particularly appropriate for climatic zone II for Europe and Japan.⁴ This is also supported by the requirements delineated in the official European stability references.^{5,6} Therefore, the continued use of 60% relative humidity for products marketed in Europe and Japan is technically justified.

Tightened requirements in Europe and Japan would mean that some container configurations would require modification to increase the water loss barrier, such as increased material thickness or selection of new materials. Such changes would have an unwarranted and significant impact on product design, cost, user features, manufacturability, waste, and natural resources utilized, with no offsetting benefits. These trade-offs should be considered as part of the decision making process.

Task force member firms are not members of PhRMA and have no direct means for participating in the ICH discussions. We believe that similar circumstances may exist in Europe and Japan and note, that to our knowledge, LVP manufacturers in these regions have not visibly participated in discussions for plastic container systems. We question the appropriateness of defining stability conditions for such products without direct input from industry.

The task force continues to be willing to conduct studies at 40% RH if the products are commercialized in the U.S. If the product is to be marketed in all three regions, a single set of studies at 40% RH should be acceptable to all authorities.

We recommend the relative humidity conditions for intermediate testing be consistent with the long term conditions, as is the case for other dosage forms. The conditions should not be more strenuous for weight loss than the accelerated conditions. A 12 month 40% RH condition is more stressful for most container configurations than 6 month/60% RH or 3 month/15% RH. The recommendation for 9 months of testing for water loss assessment is based upon the information presented in Sections VI and VII.D. below:

We recommend a 6 month minimum time frame at submission for long term and intermediate conditions supported by the fact that container system weight loss can be reliably characterized within a 6 month time frame. Additionally, the typical shelf-lives of solutions in plastic containers, are significantly shorter than those often associated with solid, oral dosage forms.

VI. Accelerated Conditions

The Task Force believes that container system water loss under accelerated testing at 40°C for 6 months/60% RH is comparable to that for 3 months/15% RH. The technical basis for this position was submitted to FDA and PhRMA in May, 1997. A copy of the Appendix which detailed this analysis and contains tables comparing water loss effects of various potential storage conditions is contained in the attached Appendix. We continue to support the following position as stated in our May 1997 correspondence:

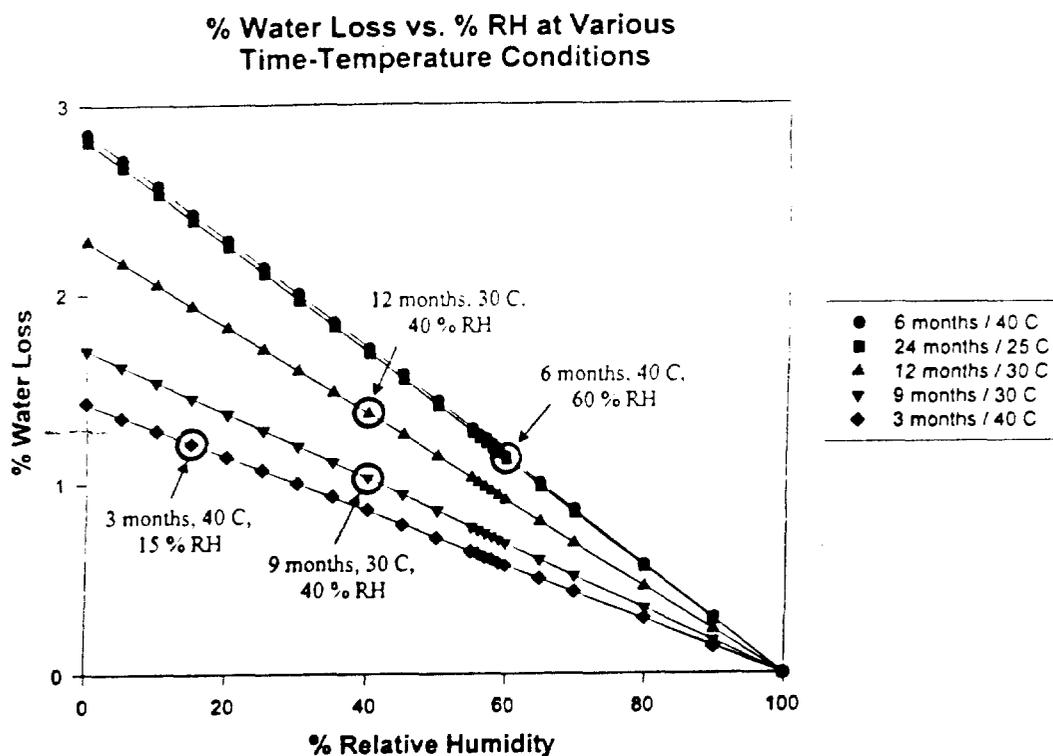
*“...The task force has previously been willing to accept 3 months/40°C/15% RH conditions. For a 6 month/40°C condition we would strongly recommend an increased relative humidity. Based upon the information presented in the attached Appendix, 60% would be an appropriate relative humidity condition for 6 months storage at 40°C. (The Appendix contains a technical discussion of the effects of time, relative humidity and temperature on water loss from plastic container systems.) The driving force for moisture loss is the pressure differential between the relative humidity within the container (approximately 100%) and the outside environment. The differential with 15% RH is 85% and with 60% RH is 40%, thus if the duration of 40°C is increased 2 fold from 3 months to 6 months, the relative humidity differential should be about doubled, consistent with the 60% RH proposal. **That is, the water loss over 6 months at 40°C/60% RH is comparable to that over 3 months at 40°C/15% RH.**”*

“An alternative approach that is also acceptable, and technically equivalent to 6 months/40°C/60% RH, would be to correct for water loss over the six month 40°C timeframe and assess water loss acceptability based on three months/40°C/15% RH. Or, alternatively, consider data which exceeds the upper concentration limit at 6 months 40°C storage due to water loss to be acceptable.”

A graphical representation of the water loss associated with various 25°C, 30°C, and 40°C temperature and time conditions as a function of relative humidity is contained in **Figure 1** below. Per the Appendix the graph represents a container system with an activation energy of 16.3 kcal/mole. The following points are illustrated:

- Water loss under accelerated 40°C conditions is comparable for 6 months/60% RH and 3 months/15% RH.
- Twelve months at 30°C/40% RH results in a greater water loss than either of the accelerated conditions and justifies our recommendation for a 9 month 30°C/40% RH intermediate assessment for products registered in all three regions.

Figure 1. Water Loss vs. % RH at Various Time-Temperature Conditions



This information justifies our proposal for accelerated testing conditions.



VII. Additional Technical Information

The applicability of the information contained in the attached Appendix to other semi-permeable plastic container systems has also been considered and is addressed in this section.

A. General Equations and Product Information

As stated in the Appendix, the water loss rate from plastic containers systems can be described by the steady-state solution of Fick's second law for diffusion through a semi-permeable material (equation 1), where Q = mass loss of water through

$$Q = AP (p_{\text{sat}} - p)t/L \quad (1)$$

the container material, P = permeability of the container material, A = surface area of the container, L = container thickness, p_{sat} = saturation vapor pressure of water inside the container, p = partial pressure of water outside the container, and t = time. Numerous similar types of mass transport processes are known to be governed by this law.^{1,2,3}

Since the relative humidity (RH) affects the partial pressure of water outside the container via.

$$p = p_{\text{sat}}(\text{RH}/100) \quad (2)$$

and the effect of temperature on the material permeability and the saturation vapor pressure is described by an Arrhenius expression, equation (1) can also be written as

$$Q = AZe^{-E/RT} (100 - \text{RH}) t / 100L \quad (3)$$

where Z = the container material and water vapor pressure combined preexponential factors, E = the container material and water vapor pressure combined activation energies, R = gas constant, and T = temperature.

Experimental data from actual containers (as shown in Appendix) have been evaluated and support the validity of equation (3). The data included experimental results in which each equation parameter (container area, thickness, temperature, relative humidity, and time) were separately varied and produced the predicted effect upon the water loss rate. Additionally, this equation correctly estimated the measured water loss found from stability studies of products conducted at 25°C/40% RH and at 40°C/15% RH.

B. Effect of Relative Humidity on Various Container Configurations

A plot from one container system (Figure 1 above) using equation (3) can be used to show that the water loss at 3 months/40°C/15% RH is a good estimate of the water loss at 6 months/40°C/60% RH. This calculation is applicable to all containers systems, since the only container-specific term in equation (3) is the material permeability. Changing the relative humidity and/or the time in equation (3) will have no influence on the material permeability, unless the material interacts (e.g. swells or reacts) with water. Such a container system would be a poor choice for parenteral solutions.

Results of weight loss studies support the validity of equation (3) with regard to estimating the impact of changing the relative humidity. The results of the first study (conducted in the U.S.) at 30% RH and 60% RH are shown below in **Table 2**.

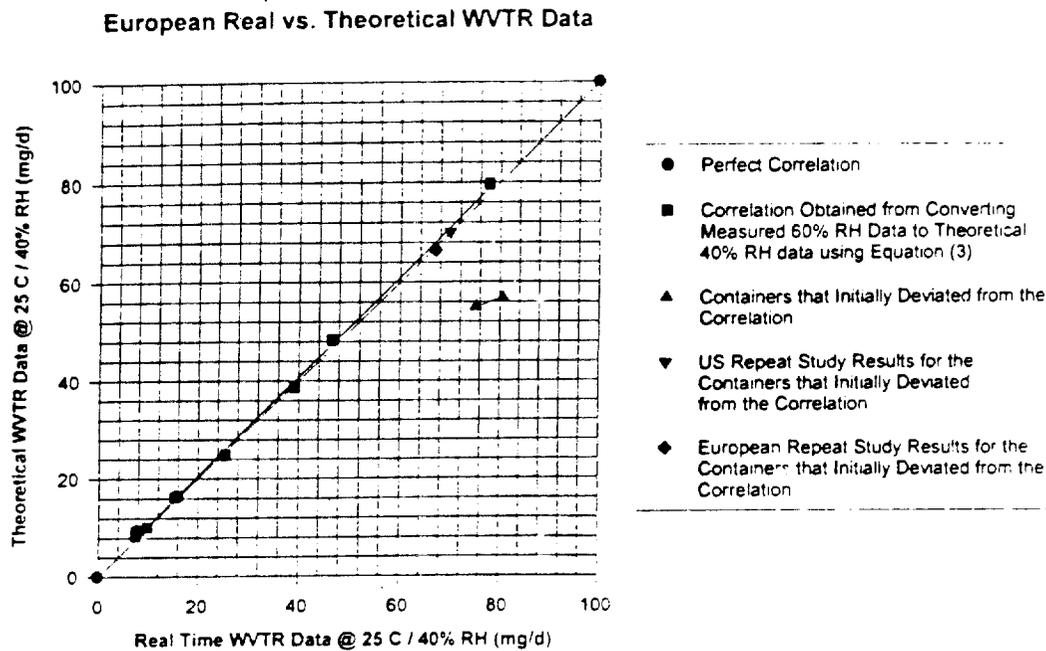
Table 2. Comparison of Water Loss at Different Relative Humidities

Container System	Water Loss Rate at 25°C/30%RH (mg/d)	Water Loss Rate at 25°C/60%RH (mg/d)	Experimental Ratio $\frac{25^\circ\text{C}/30\%\text{RH}}{25^\circ\text{C}/60\%\text{RH}}$	Predicted Ratio $\frac{25^\circ\text{C}/30\%\text{RH}}{25^\circ\text{C}/60\%\text{RH}}$
B*	44.17	24.20	1.82	1.75

*Information in Appendix regarded as first container system. 'B' designation is for second container system reported.

Another, more extensive water loss rate study was also performed in Europe. The water loss rate from thirteen different container configurations, ranging in size from 50 to 2000 mL, was evaluated at 40% RH and 60% RH over four different temperatures (25, 35, 45, and 55°C). The measured rate at 40% RH was then compared to the theoretical 40% RH value, which was calculated from the measured rate at 60% RH using equation (3). A graphical summary of the results at 25°C is shown in **Figure 2**, demonstrating agreement for the majority of the container systems. Interestingly, two of the container configurations very similar in nature deviated from the expected value and are not included in the determination of the best fit line in Figure 2. Additionally, the variation among containers was significantly larger for these two configurations. Further investigations of these container configurations at two sites were performed in order to gain a better understanding of these findings. The results of the repeat studies were in good agreement from both European and U.S. study sites and did not confirm deviation from expected behavior as initially observed.

Figure 2. Theoretical vs. Real WVTR data at 25°C/40% RH



C. Effect of Temperature on Various Container Configurations

Since the material permeability in equation (1) has a characteristic activation energy, the water loss rate at two different storage temperatures (with all other variables being held constant) may be container specific. Containers with higher activation energies would lose more water for a given temperature increase than those with lower activation energies. Therefore, containers with **higher** activation energies would require a shorter time at 40°C/15% RH to mimic the water loss over a given period of time at 25°C/40% RH.

Tables 3-5 below contain weight loss data gathered from task force member firms for a number of different plastic container systems. Fick's Law was applied to the data to determine activation energies (except where experimentally determined in the European studies described earlier), as well as the comparisons for accelerated and intermediate conditions. These tables demonstrate that the majority of these semi-permeable container systems have activation energies ranging from 14-18.6 kcal/mol. Based on these values, an accelerated condition of 3 months/40°C/15% RH corresponds to approximately the same water loss over 13-19 months at 25°C/40% RH. (An activation energy of 16.3 kcal/mole was previously determined for container system A.)

In addition, in each and every case, an intermediate condition of 12 months/30°C/40% RH corresponds to an even greater long term loss, or approximately equivalent to that over **18-20** months at 25°C/40% RH.

Therefore, although container materials do exist which have higher activation energies (see the last two container configurations in **Table 3**), an even **less stringent** accelerated or intermediate condition would mimic the room temperature conditions in these cases. For these configurations, 2 months at 40°C/15% RH corresponds to approximately the same water loss over 17 months at 25°C/40% RH.

Table 3. Firm 1

Container System	Measured Weight Loss at 25°C/33%RH (%/12 mos)	Measured Weight Loss at 40°C/10% RH (%/3 mos)	Calculated Activation Energy (kcal/mol)	Calculated Ratio 40°C/15%RH / 25°C/40%RH	Calculated Months at 25°C/40%RH equivalent to 3 months at 40°C/15%RH	Calculated Months at 25°C/40%RH equivalent to 12 months at 30°C/40%RH
C	2.13	2.24	14.10	4.43	13.3	17.8
D	1.76	1.85	14.09	4.43	13.3	17.8
E	1.41	1.53	14.49	4.58	13.7	18.0

Table 4. Firm 2

Container System	Measured Weight Loss at 25°C/40% RH (g/d)	Measured Weight Loss at 40°C/15% RH (g/d)	Calculated Activation Energy (kcal/mol)	Measured Ratio 40°C/15%RH / 25°C/40%RH	Months at 25°C/40%RH equivalent to 3 months at 40°C/15%RH	Calculated Months at 25°C/40%RH equivalent to 12 months at 30°C/40%RH
F	0.024	0.121	15.68	5.04	15.1	18.6
G	0.021	0.105	15.58	5.00	15.0	18.5
H	0.016	0.082	15.88	5.12	15.4	18.7
I	0.016	0.082	15.88	5.12	15.4	18.7
J	0.007	0.038	16.59	5.42	16.3	19.0
K	0.015	0.08	16.38	5.33	16.0	18.9
L	0.0015	0.008	16.37	5.33	16.0	18.9
M	0.0018	0.01	16.88	5.55	16.6	19.2
N	0.0065	0.056	22.30	8.61	25.8	22.4
O	0.0073	0.063	22.32	8.63	25.9	22.4

Table 5. Firm 3 (European Containers)

Container System	Measured Weight Loss at 25°C/60% RH (mg/d)	Measured Weight Loss at 45°C/60% RH (mg/d)	Measured Activation Energy (kcal/mol)	Calculated Ratio 40°C/15%RH / 25°C/40%RH	Calculated Months at 25°C/40%RH equivalent to 3 months at 40°C/15%RH	Calculated Months at 25°C/40%RH equivalent to 12 months at 30°C/40%RH
P	22.2	114.3	15.62	5.02	15.0	18.5
Q	25.7	131.9	15.53	4.98	14.9	18.5
R	10.7	60.7	16.29	5.29	15.9	18.9
S	11.0	62.7	16.54	5.40	16.2	19.0
T	31.3	175.5	16.06	5.20	15.6	18.8
U	51.3	283.3	16.12	5.22	15.7	18.8
V	42.2*	231.5*	16.00*	5.17*	15.5*	18.7*
W	6.6	30.8	16.01	5.18	15.5	18.5
X	6.5	29.1	15.65	5.03	15.1	18.6
Y	5.8	27.5	16.16	5.24	15.7	18.8
Z	6.7	43.5	18.15	6.16	18.5	19.9
AA	6.7	46.6	18.57	6.37	19.1	20.1
BB	16.3	145.7	18.45	6.31	18.9	20.1
CC	26.8	162.9	17.56	5.87	17.6	19.6
DD	24.2	150.5	17.43	5.81	17.4	19.5

* - Data from repeat studies are included for the container configuration.

D. Technical Conclusions

The water loss rate from the currently manufactured LVP containers can be accurately estimated using equation (3). The effect of time and/or relative humidity on the water loss rate is independent of the container material; therefore, the water loss at 3 months/40°C/15% RH is approximately equivalent to the water loss at 6 months/40°C/60% RH.

The effect of temperature on the water loss rate is determined by a container's characteristic activation energy, which generally ranged from 14-18.6 kcal/mol (see Tables 3-5). Although containers with higher activation energies do exist, the activation energy range of 14-18.6 kcal/mol represents a **worse case comparison** between the room temperature and accelerated conditions for the commonly used container materials. Thus, the water loss at 3 months/40°C/15% RH approximately equals the same loss over 13-19 months at 25°C/40% RH. Containers with higher activation energies need to be stored for less than 3 months at 40°C/15% RH to attain the same water loss as that incurred over 13-19 months at 25°C/40% RH).

Also, the results in Tables 3-5 can be used to evaluate intermediate stability conditions of 12 months/30°C/40% RH. **For most container configurations these conditions are even more stringent than the accelerated conditions for water loss indicating the conditions are not appropriate.** The intermediate conditions are a default condition by the ICH definition and should not be more stressful than the accelerated conditions. For

example, with an activation energy of 14.1 kcal/mol, the water loss over 9 months at 30°C/40%RH equals that over 3 months at 40°C/15%RH, and is comparable to that over 13.3 months at 25°C/40%RH. For an activation energy of 18.6 kcal/mol, the water loss over 9 months at 30°C/40%RH is comparable to that over 15.1 months at 25°C/40%RH and slightly less than that over 3 months at 40°C/15%RH. Therefore, the task force has proposed that intermediate testing conducted at 30°C/40% RH in support of marketing in the U.S. region assess water loss effects only over a 9 month period.

E. Additional Consideration

Since the effect of relative humidity on moisture loss can be easily derived, the actual relative humidity used for stability evaluations is not critical. As long as the RH is monitored, the moisture loss at the ICH RH conditions can be predicted. We believe manufacturers should retain the ability to use other, particularly lower, relative humidities if they deem appropriate. From a practical standpoint, in some areas of the United States it is very difficult to control relative humidity in stability environments to 60% RH \pm 5% RH due to the space required for LVP stability units and the changing nature of the external climate. It should be acceptable to calculate water loss at the ICH conditions based upon the actual conditions used.

It should also be acceptable to characterize container systems through separate water loss studies under ICH conditions.

VIII. Conclusions

- ◆ Although a single set of harmonized conditions for semi-permeable container systems is not practical, harmonized storage conditions can be defined which maintain acceptability of existing market containers in their marketplaces while providing technically sound guidance for all regions.
- ◆ The conditions proposed by the task force allow the continued use of 60% relative humidity in Europe and Japan and also provide for lower relative humidity conditions for the U.S.
- ◆ The conditions proposed by the task force are technically appropriate and defensible based upon data from a number of container systems, and in our opinion, also clear and durable to the practical aspects of guideline adoption in the various regions.

IX. References

- 1 - Crank, J., and Park, G.S. *Diffusion in Polymers*. New York: Academic Press, Inc., 1968.
- 2 - Bird, R.B., Stewart, W.E., and Lightfoot, E.N. *Transport Phenomena*. New York: John Wiley and Sons, Inc., 1960.
- 3 - Geankoplis, C.J. *Transport Processes and Unit Operations*. New Jersey: Prentice-Hall, Inc., 1993.
- 4 - Grimm, W., Krummen, K. "Stability Testing in the EC, Japan and the USA Scientific and Regulatory Requirements." Wissenschaftliche Verlagsgesellschaft mbH Stuttgart 1993, Pp 31-5.
- 5 - Stability Testing of new drug substances and products, CPMP, III/3335/92. December 1993.
- 6 - CPMP: Note for guidance on Stability Testing of existing active substances and related finished products, (CPMP/QWP/556/96; Draft 3, March 1997).
- 7 - HIMA letter to Roger Williams, MD and PhRMA Stability Technical Working Group, May 16, 1997.

Appendix

Copy of Appendix from May 16, 1997 Correspondence

APPENDIX: INFLUENCE OF TIME, RELATIVE HUMIDITY AND TEMPERATURE ON WATER LOSS FROM PLASTIC CONTAINER SYSTEMS

I. INTRODUCTION

Industry and regulatory authorities throughout the world have been pursuing harmonized stability conditions for pharmaceutical preparations. The class of solutions in plastic containers has been separately addressed during the discussions of ICH, because the effect of relative humidity upon product stability is the reverse of that for solid dosage forms. For solid dosage forms, increased relative humidity mediates chemical degradation. By contrast, for solutions in semi-permeable plastic containers, increased relative humidity during storage reduces the water vapor transmission rate (WVTR). Because this is the critical product parameter for LVP's, stability is apparently increased when RH is increased.

For the purposes of establishing harmonized accelerated stability conditions for this drug class therefore, it may be appropriate to first understand the influence of the relevant variables from a scientific perspective. Once this understanding has been achieved, other considerations may be overlaid upon the analysis.

II. WATER VAPOR TRANSMISSION RATE- TECHNICAL CONSIDERATIONS

The migration of water vapor through flexible plastic containers of solutions can be characterized mathematically.¹ The influence of the relevant variables of temperature, relative humidity, and time is well understood. Calculations support the conclusions that are intuitively obvious.

A. WATER LOSS VARIES LINEARLY WITH DURATION OF STORAGE. All other variables being equal, storage for six months results in twice the water vapor transmission as storage at three months.

B. WVTR VARIES LINEARLY WITH THE RH DIFFERENTIAL. All other variables being equal, what is the effect of changing the relative humidity of storage conditions? Moisture migrates from a near 100% relative humidity environment within the container, to the outside environment at some lower RH. The driving force is linearly dependent upon this differential. Using the example of increasing the relative humidity from 15% to 60%; for a 60% RH outside the container, the differential is $100\% - 60\% = 40\%$. For a 15% RH outside the container, the differential is $100\% - 15\% = 85\%$. Thus for the same study duration, storage at 15% RH results in slightly more than twice the WVTR as does storage at 60%.

¹ Stability testing and storage statement considerations for LVPs. HIMA document LVP-94-13.8. Submitted to FDA (Roger Williams, MD) October 11, 1994. Appendix contains computational detail.

C. WVTR VARIES WITH TEMPERATURE VIA THE ARRHENIUS EQU'N. All other variables being equal, what is the effect of increasing the temperature of storage from 25°C to 40°C?

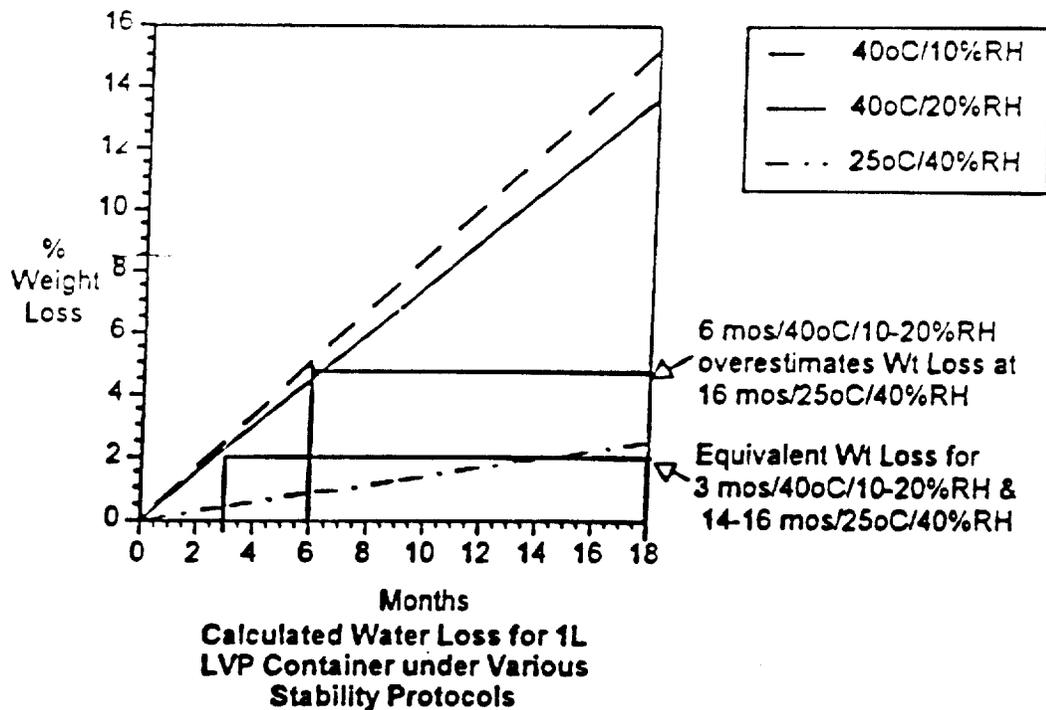
$$\frac{\text{WVTR @ } 40^{\circ}\text{C}}{\text{WVTR @ } 25^{\circ}\text{C}} = \frac{A \exp(-E/RT_{40})}{A \exp(-E/RT_{25})} = \frac{\exp(-E/1.98\text{cal} \cdot 313^{\circ}\text{K})}{\exp(-E/1.98\text{cal} \cdot 298^{\circ}\text{K})} = 3.76 \text{ fold increase}$$

This computation assumes an activation energy of 16.3 kcal/mole based upon information in the following section.

III. CURRENT ACCELERATED STORAGE CONDITIONS FOR LVP'S IN THE U.S.

The task force has previously submitted information to FDA regarding comparison of accelerated data to long term data for water loss for a representative semi-permeable container system.¹ The weight loss corresponding to current accelerated protocols of 3 months @ 40°C and 10-20% RH correlates well with that at 14-18 months @ 25°C and 40%RH.

3 MOS (NOT 6) at 40oC/10-20%RH
ACCURATELY SIMULATES
14-16 MOS/25oC/40%RH



These conclusions were confirmed by actual stability studies performed by all of the HIMA member companies which manufacture LVPs. It was established that 3

months 40°C 10-20%RH data simulate 14-18 months 25°C 40%RH storage for many products packaged in plastic containers.

Thus, for the purpose of assessing the concentration of stable chemical solutes under long-term conditions, 3 months/40°C/10-20%RH constitutes a more accurate choice than 6 months at these conditions for the expiration dating periods typically requested of these products.

Additionally, as shown in the figure above, water loss follows predictable, linear relationships; thus rates can be reliably determined within a 3 month time frame.

The agreement between accelerated and room temperature conditions can be analyzed to determine the effective activation energy for WVTR. From the data above, 3 months/40°C/10-20%RH data simulate 14-18 months 25°C/40%RH storage. One can calculate the activation energy, after first correcting for the effects of relative humidity and time. That is, WVTR at 15%RH occurs 1.42 times faster than that at 40%RH. The water lost over 16 months is 5.33 times greater than that occurring over 3 months. This results in the expression:

$$\frac{\text{WVTR @ } 40^{\circ}\text{C}}{\text{WVTR @ } 25^{\circ}\text{C}} = \frac{A \exp(-E/RT_{40})}{A \exp(-E/RT_{25})} = 5.33/1.42 = 3.756$$

Solving for E, one finds E = 16.3 kcal/mole.

IV. MATRIX FOR COMPARING WATER LOSS AT ALTERNATIVE STORAGE CONDITIONS

The variables of temperature, humidity, and time may be varied to generate additional combinations for potential accelerated storage condition protocols.

WVTR FOR VARIOUS COMBINATIONS OF RH AND TIME AT CONSTANT TEMPERATURE

Expressed Relative to WVTR at 3mos/15%RH

Time/Rel.Humidity	15%	40%	60%	75%
3 mos	X	0.7X	0.5X	0.29X
6 mos	2X	1.4X	0.94X	0.59X

This information is the basis for the recommended increase to 60% relative humidity if 6 months of 40°C testing is pursued due to its comparability with 3 months at 40°C and 15% relative humidity. The data also illustrate the task force's concern with the 6 month at 40°C/15% RH proposal, since twice the weight loss would be observed

**Draft Guidance for Industry
Stability Testing of Drug Substances and Drug Products
Specific Comments**

Attachment 3

Copy of 3/1/99 Correspondence from Dr. J. Curley

Stability of Liquid or Suspension Products Stored in Semi-Permeable Containers

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Revised after meeting with PhRMA, HIMA, and FDA
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1 March 1999

1 Additional stability considerations apply to solutions or suspensions that are stored in
2 semi-permeable containers. Semi-permeable containers allow the passage of solvent,
3 usually water, while preventing solute loss. The mechanism for solvent transport occurs by
4 dissolution into one container surface, diffusion through the bulk of the container material,
5 and desorption from the other surface. Transport is driven by a partial-pressure gradient.
6 Examples of semi-permeable containers include plastic bags or semi-rigid LDPE pouches for
7 LVPs, LDPE ampoules or bottles, and vials or bottles and nose drops in small plastic
8 containers.

9 In addition to the usual thermal considerations for assessing product stability,
10 semi-permeable containers need to be evaluated for potential solvent loss. Solvent loss
11 over time results in increased concentration of solutes in the product <>and a decrease in
12 volume in the container<>. Only water loss is considered in these discussions. Similar
13 approaches may be developed for non-aqueous solvents.

14 For aqueous products, the thermal stability characteristics of the drug product are
15 independent of the relative humidity at which the product is stored. The potential loss of
16 water is dependent on the temperature and the relative humidity, and hence the water vapor
17 differential inside and outside the container, at which the product is stored. Additional factors
18 influencing water loss are the permeability of the container material and the surface area and
19 thickness of the container as governed by Fick's second law for diffusion.^{1, 2, 3}

20 1. Stability programs for products in semi-permeable containers should evaluate both water
21 loss and chemical stability of the product. ~~Chemical stability is determined as for other~~
22 ~~products by evaluation under standard, prescribed conditions.~~ The effects of water loss
23 should be investigated at standard test conditions and under a stress condition of
24 reduced humidity. Chemical stability is determined as for other products by evaluation
25 under standard, prescribed conditions.

26
27 *[Editorial note. Two approaches have been suggested. They are designated as Proposal A*
28 *and Proposal 1. Both are presented for review and comments.]*

29
30 **Proposal A**

31

¹ Crank, J. And Park, "G.S. *Diffusion in Polymers*. New York: Academic Press, Inc., 1968

² Bird, R.B., Stewart, W.E. and Lightfoot, E.N. *Transport Phenomena*. New York John Wiley and Sons, Inc., 1960

32 Conditions Minimum time period at submission

Long Term 25°C ± 2°C/40% RH ± 5%RH 12 months

34 Accelerated 40°C ± 2°C/ ~~20% RH ± 5%RH~~ NMT 25% RH ~~6 months~~

add above

35 An alternate approach is to perform the studies, including water loss, under higher relative
36 humidities than those specified above, and derive the water loss at the specified relative
37 humidities through calculation. For example, water loss data obtained at 25°C/60%RH could
38 be used to calculate the water loss at 25°C/40%RH for the same container (same material,
39 size and fill). The assay, expressed as concentration, measured at 25°C/60%RH is adjusted
40 accordingly to reflect the concentration expected at 25°C/40%RH on which the expiration
41 date is based. This approach would allow the use of chambers currently specified for
42 storage of solid products.

43
44 Significant change at 40°C during 6 month storage (except where noted below) is defined as:

45
46 ~~1. Water loss in 3 months at or equivalent to 20%RH or in 6 months at 40%RH that is~~
47 ~~sufficient to cause a 5% increase in concentration or a decrease in volume to less than~~
48 ~~the specified amount to deliver the doses claimed:~~

49
50 1. Water loss not greater than 5% in 3 months at or equivalent to NMT ²⁵~~20~~%RH or in 6
51 months at 60%RH.

³ Geankopolis, C. J. *Transport Process and Unit operations*. New Jersey; Prentice-Hall, Inc. 1993

- 52 2. A 5% loss from initial active ingredient assay value after ~~correction~~ <>accounting<> for
water loss.
- 54 3. Any specified degradant exceeding acceptance criteria after ~~correction~~ <>accounting<>
55 for water loss
- 56 4. The product outside its pH ~~acceptance criteria~~ <>limits.<>
- 57 5. Failure to meet specifications for appearance and physical properties.

58

59 Where a significant change other than water loss occurs during accelerated conditions,
60 additional testing at an intermediate, well-defined and controlled temperature. <>The
61 purpose of this intermediate testing is to evaluate thermal or other effects, thus water loss
62 assessment is not conducted<>. A significant change in water loss alone will not necessitate
63 an intermediate study; but ~~does indicate the inadequacy of the container/closure system for~~
64 ~~both long term storage and short term excursion.~~ <>it should be demonstrated that such a
65 change does not occur over the proposed shelf life of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\% \text{RH} \pm 5\% \text{RH}$ either by
66 direct measurement of water loss at this condition or from conversion from water loss
67 observed at an alternate humidity condition. If significant change occurs at long-term
68 condition over the proposed shelf life, the container/closure system may not be adequate.<>

69 The initial Registration Application should include a minimum of 6 months' data from a 12
70 month study.

[Editorial note. Text continues from Line 22.]

Proposal 1

..... The effects of water loss should be investigated at standard test conditions
72 as well as under a stress condition of reduced humidity.

73

74 This may be done by monitoring the weight change in one batch of either product or a worst
75 case simulation over a three month period at a condition of 40°C±2°C NMT 25%RH. A
76 significant change in water loss at 40°C±2°C NMT 25%RH has occurred if after 1 month the
77 loss in water would be sufficient to cause the potency to exceed its upper concentration
78 specification limit or to decrease the volume within the container to less than an amount
79 sufficient to deliver the doses claimed. If a significant change in water loss occurs at
80 40°C±2°C NMT 25%RH, then the applicant must demonstrate that a significant change in
81 water loss does not occur if the product is stored at the proposed long term storage
82 temperature at a relative humidity NMT 40%RH. This may be done by either testing the
83 product at a long term storage condition of 25°C±2°C/40%RH±5%RH or by calculating the
84 moisture loss at 40%RH for the long term storage temperature based upon long term storage
85 at an alternative relative humidity, for example 25°C±2°C/60%RH±5%RH.